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PRINCIPAL INVESTIGATOR:
Ajit K. Verma Ph.D.

CONTRACTING ORGANIZATION:
University of Wisconsin, Madison, WI 53792

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Ajit K. Verma Ph.D.

E-Mail: akverma@facstaff.wisc.edu

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14. ABSTRACT

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The objectives of this proposal are to determine whether protein kinase C epsilon (PKCε) is linked to the initiation and progression of Prostate cancer (PCa) and should be explored as a molecular target for the prevention of human PCa. PKCε, a calcium-insensitive PKC, is among the PKC isoforms expressed in both mouse and human prostate tissue. We plan to test the hypothesis that PKCε is linked to the onset, progression and metastasis PCa. Two specific aims are proposed to test this hypothesis. Specific Aim #1: To obtain the first molecular genetic evidence that PKCε is linked to the development of PCa. To accomplish this specific aim, we will employ TRAMP mice, the well-established mouse model of PCa. We will deplete PKCε in TRAMP mice by crossbreeding TRAMP mice with PKCε knockout (-/-) mice. We will evaluate TRAMP-PKCε KO mice for the development and progression of PCa *in vivo*. We will determine whether the genetic loss of one (-/+) or both (-/-) PKCε alleles will attenuate the progression of PCa. Specific Aim #2: To explore the mechanisms by which PKCε may promote the progression of AI PCa. This report will review the accomplishments made over the third year of grant award with respect to these specific objectives and according to the time line proposed in the original statement of work of the project.

15. SUBJECT TERMS
Prostate Cancer, androgen-dependent, androgen-independent, Protein kinase C epsilon, transgenic adenocarcinoma of mouse prostate, interleukin

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ANNUAL REPORT FOR AWARD NUMBER " W81XWH-07-1-0049"

ENTITLED MOLECULAR TARGETS FOR PREVENTION OF PROSTATE CANCER.

FUNDING PERIOD: December 1, 2008-December 31, 2009-Final revised report

Dr. Ajit K. Verma, Ph.D.
Professor
Department of Human Oncology
University of Wisconsin Medical School
K4/532 Clinical Science Center
600 Highland Avenue
Madison, WI 53792
Phone: (608) 263-9136
Fax: (608) 262-6654
E-mail: akverma@facstaff.wisc.edu

INTRODUCTION

Prostate cancer (PCa) is the second leading cause of cancer-related deaths in men. The risk of PCa increases rapidly after age 50 in men, with two-thirds of all PCa cases found in men after age 50. PCa first manifests as an androgen-dependent (AD) disease and can be treated with androgen-deprivation therapy.

Despite the initial success of androgen ablation therapy, PCa progresses from AD to androgen-independent (AI). The hormone refractory, invasive PCa is the end stage and accounts for the majority of PCa patient deaths. Defining the molecular mechanisms linked to the transition of AD PCa to a hormone refractory PCa is essential in planning strategies in the prevention and treatment of PCa. The objectives of this proposal are to determine whether protein kinase C epsilon (PKCε) is linked to the initiation and progression of Prostate cancer (PCa) and should be explored as a molecular target for the prevention of human PCa. PKC represents a family of Phospholipid-dependent, serine/threonine protein kinases.

PKCε is a calcium-insensitive PKC. Previous studies have shown, using cultured prostate cancer-derived cell lines and human PCa specimens that PKCε may play a role in the progression to AI PCa. However, the role PKCε plays in the course of PCa progression on the whole tissue level *in vivo* is unknown and that forms the focus of this proposal. We plan to test the hypothesis that PKCε is linked to the onset, progression and metastasis PCa. Two specific aims are proposed to test this hypothesis: **Specific Aim #1:**To obtain the first molecular genetic evidence that PKCε is linked to the development of PCa. To accomplish this specific aim, we will employ TRAMP mice. **Specific Aim #2:** To explore the mechanisms by which PKCε may promote the progression of AI PCa. PKCε may be a new marker for the prognosis of PCa, as well as a molecular target for the prevention and therapy of PCa. Knowledge obtained from the proposed study will help to plan strategies to manage the development of PCa.

BODY (Key Research Accomplishments by original statement of work

***Task 1*: Specific Aim #1: To obtain the first molecular genetic evidence that PKCε is linked to the development of PCa**.

The principle experimental approach to link PKCε to the development of PCa is to deplete PKCε in TRAMP mice. This was accomplished by crossbreeding TRAMP mice with PKCε knockout (-/-) mice. We evaluateed TRAMP- PKCε KO mice for the development and progression of PCa *in vivo.* We determined whether genetic loss of one (-/+) or both (-/-)PKCε alleles attenuated the progression of PCa. Following experiments are performed:

Generation and characterization of PKCε deleted TRAMP mice: As shown in Figure 1A, TG, Het and KO mice were generated by cross-breeding 6-7 wks old homozygous TRAMP with PKCε-heterozygous (Het) mice (Fig.1A). Both TRAMP and PKCε KO mice were on FVB/N background. No PKCε expression was observed either in prostate or brain excised tissues of KO mice (Fig.1B-C). A significant decrease in protein levels of PKCε was observed in the prostate of Het mice compared to TG mice (Fig.1B). To determine whether deletion of PKCε has any compensatory effect in TRAMP mice, we performed immunoblot analysis of PKC isoforms in prostate and brain tissue lysates of TG, Het and KO mice. Results indicate no change in the expression of other PKC isoforms in brain tissue of Het and KO mice (Fig. 1Ci-ii) suggesting no compensatory effects in PKCε-deleted TRAMP mice.

Deletion of PKCε in TRAMP mice inhibits PCa development and metastasis. Accumulating evidence now indicates that PKCε is an oncogene, which plays a vital role in the development of various types of human cancers including the prostate. Molecular genetic evidence of the role of PKCε in PCa development in an intact mouse model still remains obscure. In this study, we explored the possibility whether PKCε deletion in TRAMP mice inhibits the development and metastasis of PCa. A total of 21 mice (TG: n=7, Het: n=7, and KO: n=7) were used in this study. In our first experiment, we performed MicroPET/CT imaging, using a tumor selective radiopharmaceutical agent ^{124}I-NM404 (16), of two 16 wks old mice from each of TG, and KO mice (Fig.2Ai-Bi). Results illustrated a lack of focal uptake of ^{124}I-NM404 in KO mice (Fig 2Bi-ii), compared to TG mice (Fig.2Ai-ii). TG mice showed metastasis in proximal lymph node as evident by uptake of ^{124}I-NM404 (Fig.2Ai-ii). However, no metastasis was observed in KO mice, suggesting the role of PKCε in the development and metastasis of PCa. All of the remaining mice from each group were sacrificed at the same age (18 wks). Their bloods were collected from retro-orbital plexus for serum isolation. PCa tissues were excised and parts of the tissues were used in preparation of whole tissue lysates, nuclear lysates, RNA isolation, and for histology sectioning as described in methods. Parts of the tissues excised from the kidneys, brains, livers, lungs and lymph nodes were fixed in 10% buffered formalin and used for histopathology. Deletion of PKCε in TRAMP mice, or even one allele deletion shows significant ($P<0.01$) reduction in growth of PCa in all of the Het and KO mice (Fig.2C-D). All TG mice developed one or two large-sized prostate tumors (Fig.2C-TG), while Het and KO mice had only a single small-sized tumor (Fig.2C-Het and KO). One of the TG mice also showed grossly visible

metastases in a local lymph node, both lungs, and the left kidney, which were confirmed by light microscopy (Fig.2E-F). In additional, microscopic metastases were indentified in another three TG mice. No metastasis was indentified in any of the Het and KO mice (Fig.2G-H). H&E-stained tissue sections demonstrated that all the grossly visible tumors were poorly differentiated (P.D.) carcinomas characterized by solid sheets of large polymorphic cancer cells with a high nucleus to cytoplasm ratio, frequent apoptosis, central necrosis, and neuroendocrine differentiation (Fig.3Di and Ei). Some of the Het and KO mice showed small foci of P.D. carcinoma at the microscopic level only. In additional, all the mice showed prostatic intraepithelial neoplasia (PIN) characterized by epithelial cell proliferation with enlarged hyperchromatic nuclei and nuclear stratification in papillary and cribriform structures (Fig.3Di and Ei).

Task 2: **Specific Aim #2: To explore the mechanisms by which PKCε may promote the progression of AI PCa. Anticipated time to accomplish: 24-36 months**

Deletion of PKCε in TRAMP mice inhibits Stat3 activation: Aberrant activation of Stat3 has been linked to progression of PCa metastasis (17-19). A study suggests that overexpression of Stat3 in normal prostate epithetial cells leads to conversion of malignant phenotype (20). To determine whether PKCε deletion in TRAMP mice inhibits Stat3 activation, we performed immunoblot analysis in excised tissue PCa lysates of TG, Het and KO mice. Results illustrated significant inhibition of both Ser727 and Tyr705 phosphorylation of Stat3 in both Het and KO mice (Fig.3A). A significant decrease in DNA binding activity of Stat3 was observed in Het and KO mice (Fig. 3 Bi-ii). Immunohistochemistry results demonstrate a significant decrease in intensity of nuclear staining of Stat3 in PIN and poorly differentiated PCa of KO mice (Fig.3C, Eii) compared to TG mice (Fig.3 Dii). Specificity of Stat3 staining in TG PCa tumor tissue was confirmed by using blocking peptide of Stat3 (Fig.3F).

Deletion of PKCε inhibits serum interleukin-6 (IL-6) and IL-6 receptor gp130 expression: We have previously shown elevated levels of IL-6 in TRAMP mice compared to non-transgenic mice at the same age (14). To determine whether deletion of PKCε in TRAMP mice decreases serum IL-6 levels, we performed specific ELISA for mouse IL-6 and observed a significant ($P<0.05$) decrease in serum IL-6 levels in Het and KO mice compared to TG mice (Fig.4H), suggesting that PKCε might be initiator of the IL-6/Stat3 signaling pathway. IL-6 receptor (gp130) is one of the downstream target genes of Stat3. Immunohistochemistry results demonstrated a significant decrease in the protein levels of IL-6R in KO mice compared to TG mice (Fig.4A).Weak immunostaining of IL-6R was observed in benign epithelial cells and moderate staining in poorly differentiated carcinoma cells of both TG and KO mice (Fig.4Ei), while there is strong immunostaining of IL-6R in PIN of TG mice and only moderate staining in PIN of KO mice (Fig.4Di). Specific immunoreactivity of IL-6R was confirmed by using blocking peptide of IL-6R antibody (Fig.4Fi).

Deletion of PKCε inhibits markers of proliferation, and anti-apoptosis and metastasis: Evidence from published studies, including our laboratory, suggests modulation of various apoptotic and proliferative biomarkers in PCa in both humans and TRAMP mice during the progression and metastasis (14, 21). To determine possible changes in biomarkers involved in apoptosis, proliferation, and metastasis of PCa in PKCε-deleted TRAMP mice, we performed immunoblot analysis of selected biomarkers in PCa tissue lysates of TG, Het and KO mice. We observed a decrease in the protein levels of BclxL, COX-2, cyclin D1, and VEGF in Het and KO mice (Fig.4A-B). We have previously shown overexpression of PI3K/AKT in PCa tissues of TRAMP mice compared to non-transgenic prostate tissues at the same age (14). We observed a decrease in the protein levels of PI3K85 in Het and KO mice, but no change was observed in the protein levels of PI3K110 (Fig.4B), pAKTSer473 and pAKTSer308 (Fig.4C). We also performed immunohistochemistry of PCNA in PCa tissues of TG

and KO mice, and observed a significant decrease in the nuclear levels of PCNA in PIN and poorly differentiated PCa of KO mice (Fig. 4Eii-4G).

qPCR array identifies decreased transcripts of genes implicated in PCa development and metastasis: To further define the role of PKCε in modulating the other genes associated with JAK/STAT3 signaling and involved in PCa development and metastasis, we performed qRT-PCR array of genes associated with JAK/STAT signaling pathway on total RNA isolated from PCa tissues of TG and KO mice. This array contained 84 genes related to JAK/STAT family members, the receptors that activate them, nuclear co-factor and co-activators associated with the Stat proteins, Stat inducible genes, and negative regulators. A significant decrease in the m-RNA expression of CCAAT/enhancer binding protein (CEBP) β (2.5 fold), C-reactive protein (4.34 fold), epidermal growth factor receptor (EGFR) (4.54 fold), gp130 (2.5 fold), jun B (2.5 fold), and Stat3 (2.85 fold) was observed in KO mice compared to TG mice (Table 1). These results indicate that PKCε directly and/or indirectly regulates the expression of Stat3 and Stat3 downstream target genes involved in PCa development and metastasis.

Figure 1. Generation and characterization of PKCε deleted TRAMP mice. (A): Scheme for generation of bigenic PKCε KO TRAMP mice. Both TRAMP and PKCε KO mice were on FVB/N background. TG, Het and KO mice were evaluated for the development of PCa. (**B and C):** Western blot analysis of PKC expression in PCa and brain tissues lysates (40 µg protein) from 18 wks old TG, Het and KO mice. Protein levels of PKCε and PKCα in PCa tissues (**B)** and PKC isoforms in brain tissues **(Ciii)**. Equal loading of protein was determined by stripping and reprobing the blots with β-actin antibody. Values (arbitrary number) shown above the immunoblots represent densitometer quantitation of band normalized to β-actin.

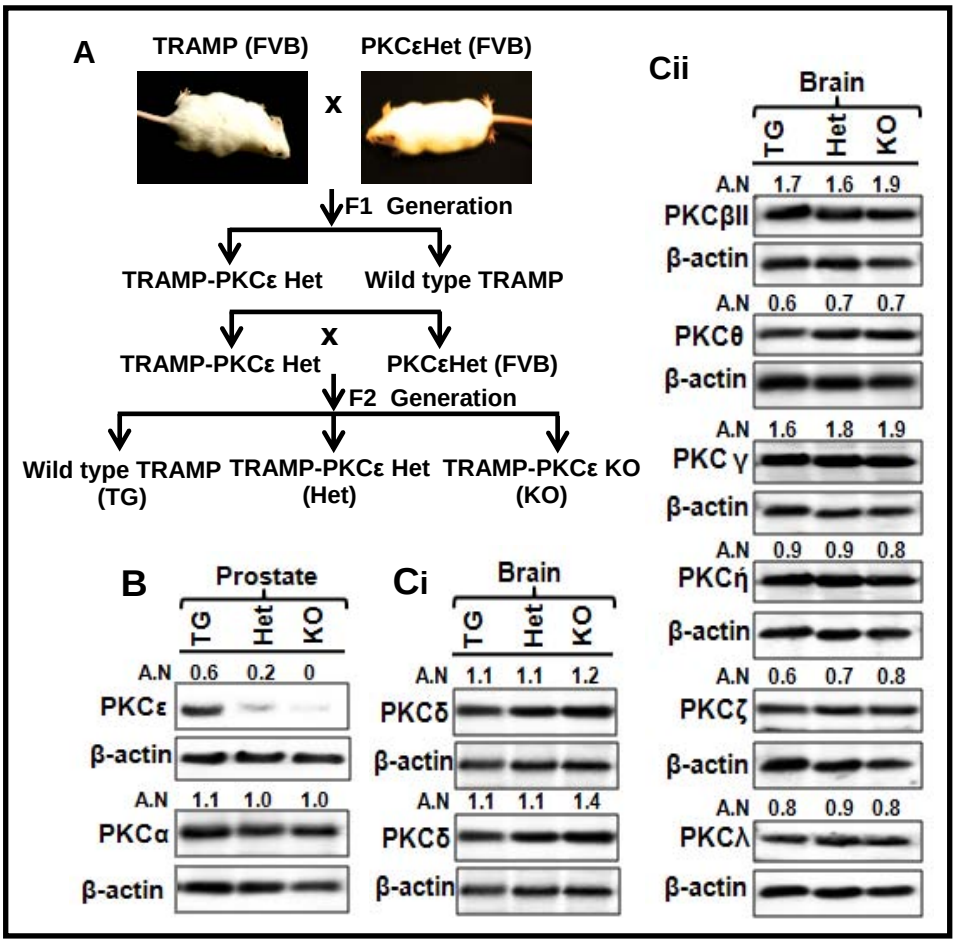
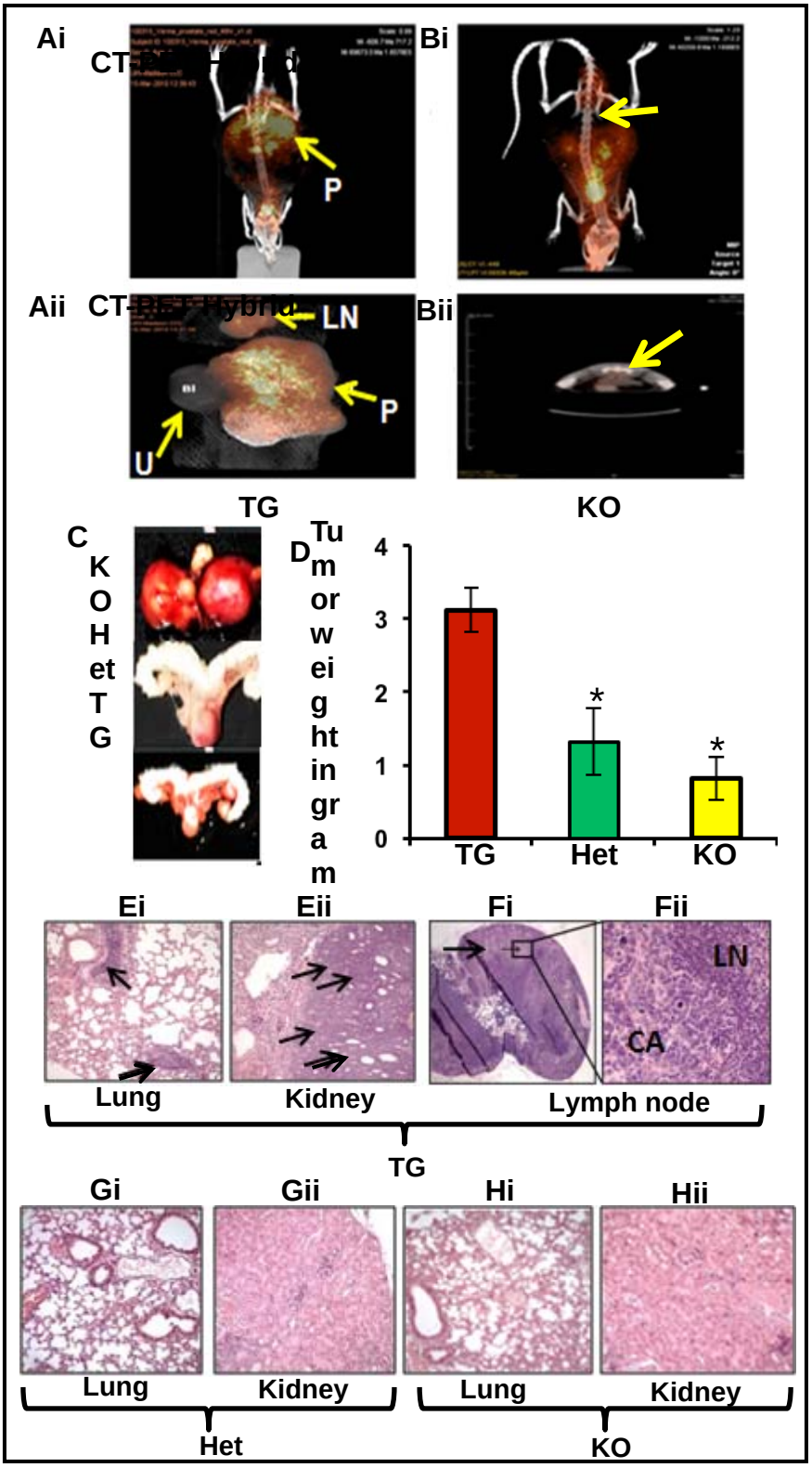


Fig. 1

Figure 2. Deletion of PKCε in TRAMP mice inhibits development and metastasis of PCa. TG (N=5), Het (N=5), and KO (N=5) male mice were evaluated for the development of PCa. Hybrid microPET/CT image acquired 48h post $^{124}I^{-}$INM404 iv injection to TG **(A),** and KO **(B)** mice at 18 wks. Hybrid microPET/CT images of excised prostate tumor of TG **(Ai),** and KO mice **(Bi)**. U, LN, and P denote to urinary bladder, proximal lymph node and PCa respectively. **(C)**: Representative pictures of excised urogenital tracts of TG, Het and KO mice at 18 wks. **(D)**: Bar graph illustrates excised prostate tumor weight of TG, Het, and KO mice. Each value in the bar graph represents Mean ± S.E.M. of five different mice. Student's t-test was performed to evaluate the significant difference ($P<0.01$). Representative photographs of H&E staining of lung **(Ei)**, kidney **(Eii)**, and lymph node **(Fi-ii)**. Enlarge image of lymph node (**Fi**) showing normal lymphocytes and PCa metastases **(Fii)**. Arrows indicate metastases of PCa in the lung, kidney, and lymph node of TG mice. Representative photographs of H&E-stained tissue sections of lung **(Gi)** and kidney **(Gii)** of Het mice, and lung **(Hi)** and kidney **(Hii)** of KO mice.


Ai
CT-
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Aii
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Hybrid
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U
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TG
KO
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TG
Het
KO
Ei
Eii
Fi
Fii
LN
CA
Lung
Kidney
Lymph node
TG
Gi
Gii
Hi
Hii
Lung
Kidney
Lung
Kidney
Het
KO

Figure 2

Figure 3. Deletion of PKCε in TRAMP mice inhibits Stat3 activation. PCa tissues from TG, Het and KO mice were excised and whole cell lysates were prepared and used for Western blot analysis as described in material and methods. **(A):** Protein levels of pStat3Tyr705, pStat3Ser727 and total Stat3. Equal loading of protein was determined by stripping and reprobing the blots with β-actin antibody. Values (arbitrary number) above the immunoblots represent quantitation of the bands normalized to β-actin as described in material and methods. **(Bi):** DNA binding activity of Stat3 in PCa tissues of TG, Het and KO mice as determined by electromobility shift assay (EMSA). Lane 1 is free probe. Specificity of Stat3 DNA binding was determined by mutant probe of Stat3 (Lane 2). **(Bii):** Quantitative analysis of EMSA of Stat3 DNA binding activity of TG, Het and KO mice. **(C):** Bar graph represents quantification of Stat3 nuclear staining of TG and KO prostate tumor tissues. Student t-test was performed to analyze nuclear staining difference ($P<0.05$). **(Di-Eii):** Representative photographs of (H&E) staining and immunohistochemistry of Stat3 in Benign Prostate (B.P) Epithelium, Prostatic Intraepithelial Neoplasia (PIN) and Poorly Differentiated (P.D) Adenocarcinoma of TG and KO mice. Arrows indicate the nuclear staining of Stat3. **(F):** Specificity of Stat3 antibody by using Stat3 blocking peptide.

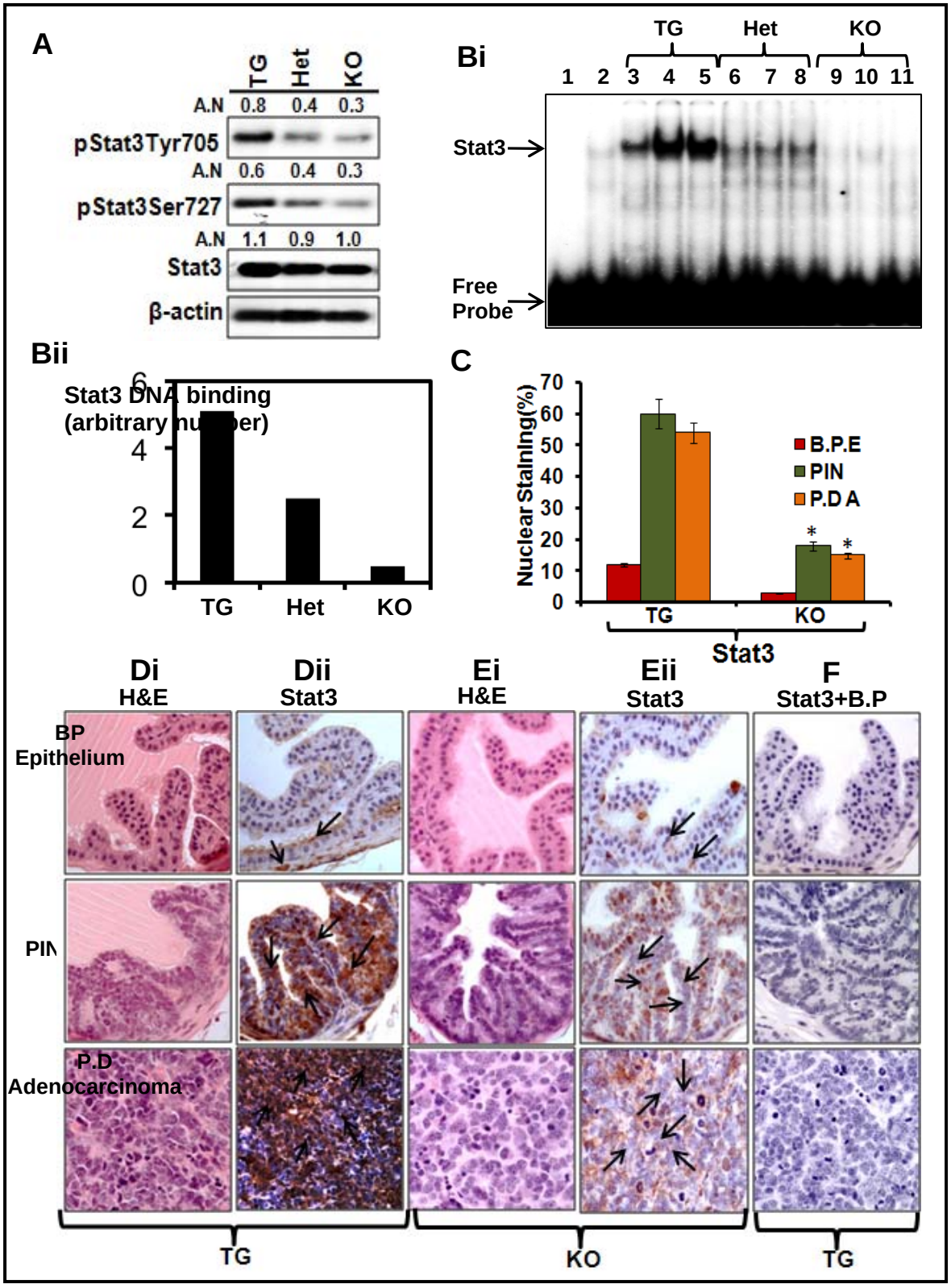
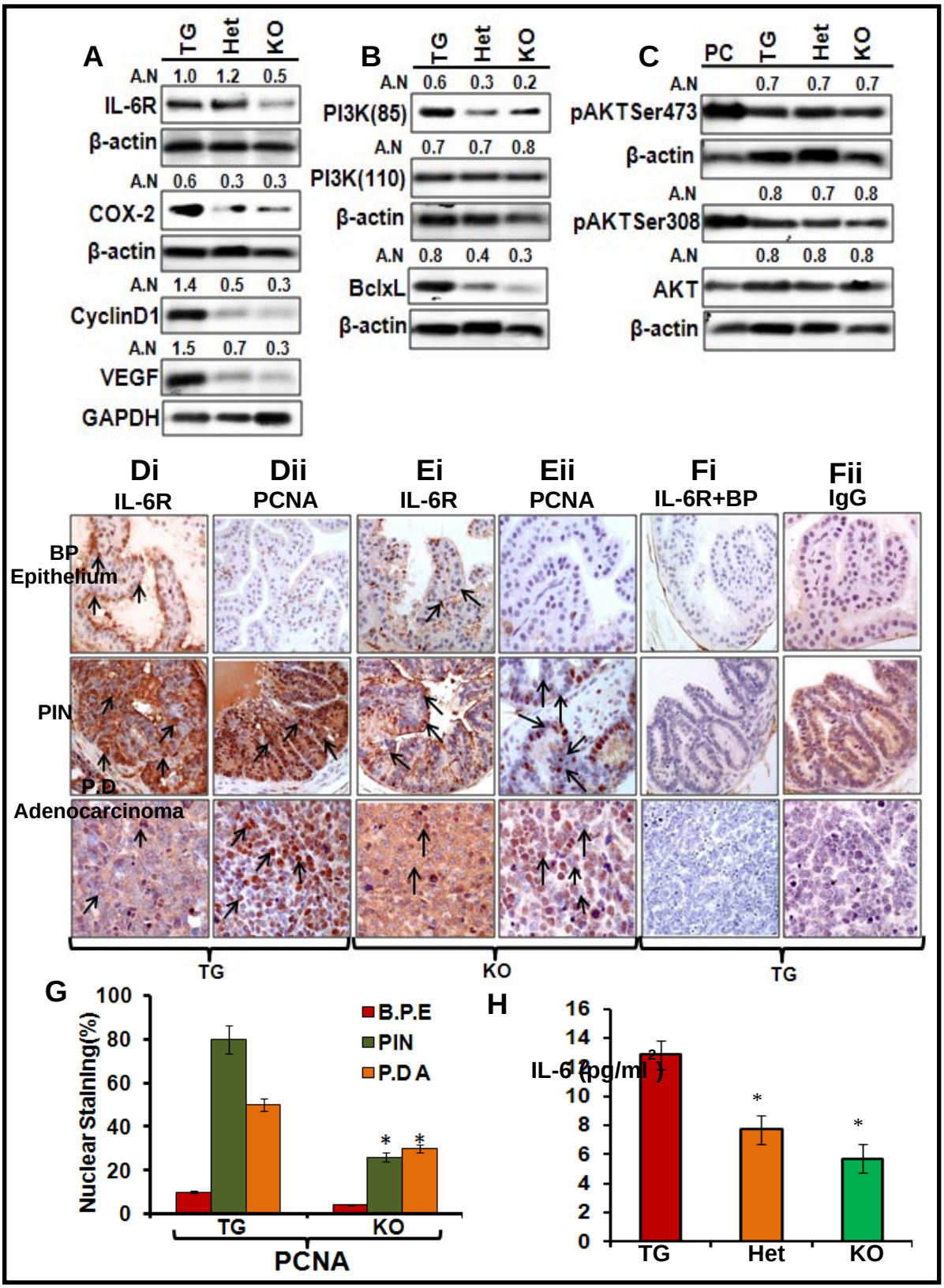

A
TG
Het
KO
A.N 0.8 0.4 0.3
pStat3Tyr705
A.N 0.6 0.4 0.3
pStat3Ser727
A.N 1.1 0.9 1.0
Stat3
β-actin
Bi
TG
Het
KO
1 2 3 4 5 6 7 8 9 10 11
Stat3
Free Probe
Bii
Stat3 DNA binding (arbitrary number)
6
4
2
0
TG
Het
KO
C
Nuclear Staining(%)
70
60
50
40
30
20
10
0
B.P.E
PIN
P.D A
*
*
TG
KO
Stat3
Di
H&E
Dii
Stat3
Ei
H&E
Eii
Stat3
F
Stat3+B.P
BP Epithelium
PIN
P.D Adenocarcinoma
TG
KO
TG

Fig. 3

Figure4. Deletion of PKCε in TRAMP mice inhibits expression of anti-apoptotic and proliferative markers and decreases serum IL-6 level. PCa tissues of 18 wks old TG, Het and KO mice were excised and homogenized in the lysis buffer for Western blot analysis as described in material and methods. Proteins (40 µg) were subjected on 10-15% Tris-Hcl SDS-PAGE and immunoblotted using appropriate antibodies. Equal loading of protein was determined by stripping and reprobing the blots with β-actin or GAPDH antibodies. Values (arbitrary number) above the immunoblots represent quantitaion of the bands normalized to β-actin or GAPDH as described in material and methods. **(A):** Expression level of IL-6R), COX-2, Cyclin D1, and VEGF. **(B):** Expression of PI3K (85) and PI3K (110) and BclxL. **(C):** Expression level of pAKTSer473, pAKTSer308 and total AKT. **(D-E):** Representative photographs of immunohistochemistry of IL-6R and PCNA in Benign Prostate Epithelium (B.P), Prostatic Intraepithelial Neoplasia (PIN) and Poorly Differentiated Adenocarcinoma (P.D) of TG (Di-Dii) and KO (Ei-Eii) mice. Arrows indicate immunoperoxidase labeling of IL-6 and PCNA. **(Fi)**: Specificity of IL-6 antibody by using IL-6 blocking peptide. **(Fii):** Negative control by using IgG **(G)**: Bar graph represents quantification of PCNA nuclear staining in B.P, PIN, and P.D. of TG and KO mice. Student t-test was performed to analyze nuclear staining difference ($P<0.05$). **(H):** Serum IL-6 levels as determined by ELISA kit for mouse IL-6. Each value in the Bar graph represents the Mean ± SEM of IL-6 level from 3 mice. Results indicate a significant decrease ($P<0.05$) in the levels of serum IL-6 in Het and KO mice compared to TG mice.


A
TG
Het
KO
A.N 1.0 1.2 0.5
IL-6R
β-actin
A.N 0.6 0.3 0.3
COX-2
β-actin
A.N 1.4 0.5 0.3
CyclinD1
A.N 1.5 0.7 0.3
VEGF
GAPDH
B
TG
Het
KO
A.N 0.6 0.3 0.2
PI3K(85)
A.N 0.7 0.7 0.8
PI3K(110)
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β-actin
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β-actin
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pAKTSer308
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AKT
β-actin
Di
IL-6R
Dii
PCNA
Ei
IL-6R
Eii
PCNA
Fi
IL-6R+BP
Fii
IgG
BP
Epithelium
PIN
P.D
Adenocarcinoma
TG
KO
TG
G
Nuclear StaInIng(%)
100
80
60
40
20
0
B.P.E
PIN
P.D A
*
*
TG
KO
PCNA
H
IL-6 (pg/ml)
16
14
12
10
8
6
4
2
0
*
*
TG
Het
KO

Fig. 4

Table1: Deletion of PKCε in TRAMP mice modulates IL-6/Stat3 signaling associated genes involved in PCa progression and metastasis. Focused qPCR array for JAK/STAT signaling pathway was performed in TG and KO PCa as described in materials and methods. Table represents the fold increase or decrease of mRNA expression JAK/STAT signaling associated genes in KO mice compared to TG mice.

Table1: List of genes that significantly modulated in KO mice compared to TG mice:

No of genes down-regulated gene in KO mice compared to TG mice:			
Name of the gene	**Symbol**	**Gene description**	**Fold decrease/ increase**
CRP2	Cebpb	CCAAT/enhancer binding protein (C/EBP), beta	2.5
Al255847	Crp	C-reactive protein, pentraxin-related	4.34
CMK	CxCL9	Chemokine (C-X-C motif) ligand 9	2.94
ERBB	EGFR	Epidermal growth factor receptor	4.54
Epor	Epor	Erythpoietin receptor	3.57
CD64	Fcgr1	Fc receptor, IgG, high affinity I	2.56
UCRP	Isg15	ISG15 ubiquitin-like modifier	3.0
GHR	Ghr	Growth hormone receptor	2.77
mIL-10R	ll10ra	Interleukin 10 receptor, alpha	3.12
IL-10R2	ll10rb	Interleukin 10 receptor, beta	3.70
CD132	ll2rg	Interleukin 2 receptor, gamma chain	2.70
CD124	ll4ra	Interleukin 4 receptor, alpha	2.22
gp130	ll6st	Interleukin 6 Signal transducer	2.5
JunB	JunB	Jun-B Oncogen	2.5
L3	Oas1a	2'-5' oliogoadenylate synthetase 1A	2.22
CD140a	Pdgfra	Platelet derived growth factor receptor, alpha polypeptide	2.70
Cd45	Ptprc	Protein tyrosine phosphatase, receptor type, C	2.77
SOCS-1	socs1	Suppressor of cytokine signaling 1	2.63
Aprf	Stat3	Signal transducer and activator of transcription 3	2.85
No of genes down-regulated gene in KO mice compared to TG mice:			
ll-4	ll4	Interleukin 4	2.26
AP-1	Jun	Jun-Oncogene	2.83
Pr-1	prlr	Prolactin Receptor	3.58

Table1

REPORTABLE OUTCOMES

A publication. One published one submitted
Patents and licenses – NONE
Degrees obtained – NONE
Development of cell lines, tissue or serum repositories – NONE
Informatics – NONE
Funding applied for based on work supported by this award : NONE
Employment or research opportunities applied for – NONE

CONCLUSIONS

Prostate cancer is the most common type of cancer in American men and ranks second to lung cancer in cancer-related deaths. While 1 in 6 men will get prostate cancer during his lifetime, 1 in 34 will die of this disease. Prostate epithelial cells are dependent on the male hormone androgen for survival and enter programmed cell death following hormone oblation resulting in involution of the prostate gland. Early PCa is typically diagnosed as androgen-dependent and is treated with anti-androgen drugs or using a procedure termed castration, which involves removal of the androgen producing testes. Despite androgen therapy, some of the cancer cells still survive and grow to form PCa. The PCa that grows after hormone therapy is called androgen independent (AI) PCa. This invasive PCa is the end stage and accounts for the majority of PCa patient deaths. The management of locally advanced prostate cancer is difficult and complex because the cancer often becomes hormone-insensitive and unresponsive to current chemotherapeutic agents. Knowledge about the regulatory molecules involved in the transformation to AI prostate cancer is essential for the rational design of agents to prevent and treat prostate cancer. Recently we found a protein termed protein kinase C epsilon (PKCε), which may play a role in the formation of advanced prostate cancer. The level of this protein is increased in prostate cancer tissue as compared to the normal prostate. The proposed study is aimed at validating the role of this protein in the progression of prostate cancer. Knowledge obtained from the proposed study will help to plan strategies to manage the development of PCa. This PKCε protein may be a new marker for the prognosis of PCa, as well as a molecular target for the prevention and therapy of PCa.

REFERENCES: None

APPENDICES: Three manuscript

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